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Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket No. 00D-1306 - FDA Draft Guidance for Industry on the Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics (65 Federal Register 38563; June 21, 2000)

Dear Sir or Madam:

Bristol-Myers Squibb Company (BMS) is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious disease, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1999, pharmaceutical research and development spending totaled $1.4 billion.

For these reasons, we are very interested in and well qualified to comment on this FDA proposal to issue a Guidance on the Content and Format of the Adverse Reactions Section of Labeling.

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Summary of BMS Comments

BMS supports in principle the concept of revising current US labeling to provide the prescriber with more "user friendly" information concerning the balance of benefits and risks. While the ideas expressed are of potential benefit, BMS has identified several key issues concerning the specific methods of their execution that in our opinion require additional evaluation, clarification and/or revision, particularly in relation to satisfying the differing requirements of the multiple constituencies which are affected by labeling. BMS would welcome the opportunity to work collaboratively with FDA and other interested parties to address these issues and concerns in a more innovative approach to label redesign and regulatory revision. Our major concerns focus on the following areas:

1. **Adverse Reaction vs. Adverse Event** - The proposal to distinguish between Adverse Reactions and Adverse Events has merit, but there is no consensus regarding the criteria which distinguish an event from a reaction, i.e., when the balance of probability favors a causal association. Before FDA can require labeling to include only adverse reactions, and not adverse events, there must first be standardization and uniform assessments of causality across products and FDA divisions, preferably in an internationally harmonized standard, as well as a clear definition of clinical diagnostic terms describing them to avoid subjective bias.

2. **Overview Section** - The creation of an "overview" raises various legal and clinical concerns. The manufacturer and FDA will be forced to select from among the entire body of all safety information certain "serious and important adverse reactions". This not only leads to redundant presentation of the data but also to a potential for undue exposure of the manufacturer to product liability lawsuits based on a "failure to warn" if a given event is listed in the overall adverse event experience section but not in the overview. In addition the prescriber may refer to the summary section only and may not consider other relevant events described in the body of the text. If FDA nevertheless mandates an 'overview", then at a minimum, the criteria for selecting the relatively small subset of events for presentation in the Overview section must be specified clearly to avoid arbitrary assessment of "importance" by the manufacturer and/or FDA.

3. **Implementation Timeframe & Evidence Supporting Change** - FDA proposes to issue future guidances for the format and content of other label sections containing important safety information. BMS submits that implementation of the current draft guideline prior to their availability would be less productive than waiting until all relevant guidance documents are available. In addition, evidence that the proposed changes will improve communication to prescribers of information concerning benefits and risks should be obtained prior to implementation. FDA should also consider the impact on prescribers facing differences between labels for comparable products.

4. **Scope** - The scope of this guidance requires clarification; specifically, which products will be affected (newly-approved chemical entities vs. existing products).

Introduction

BMS supports FDA's guidance document proposing revisions to current US labeling in principle but has identified the following that in our opinion require clarification and/or revision. Our comments are presented below, first in relation to general concepts, and then additional comments specific to individual sections, numbered according to the sections of the draft guidance document.

General Comments

1. The Federal Register notice (Vol. 65, No. 120 Wednesday, June 21, 2000) indicates that FDA is developing guidances for other sections of US labeling containing important safety information (*Contraindications, Warnings and Precautions sections)* as well as a change in the *Overall Format and Contents of the package insert.* BMS considers that, given the unitary nature of the safety information required for safe and effective prescribing, any revision of the Adverse Reactions section of the label should be fully coordinated and integrated with revisions to the other safety sections and that adoption and implementation of this guidance in isolation prior to the adoption of those guidance would be premature. Furthermore, we feel strongly that future guidance documents on labeling should not be implemented piecemeal, but deferred until completion of all relevant guidances and relevant regulations to minimize the number of labeling supplements that will have to be developed by industry and approved by FDA.

2. The proposals in this draft guidance, together with those that may be anticipated in future guidances concerning other label sections, will result in major changes in the format of the US label and potentially entail major revisions of numerous existing labels. However, there is no evidence that the proposed changes will achieve the desired goal of improving the communication of safety data to prescribers. BMS therefore recommends that FDA conduct surveys of the utility of the proposed new format among prescribers, if this has not already been done. If it has, the results of such surveys should be shared with the public. Absent such feedback, the concern arises that the changes might in fact impede, rather than improve, the assessment of benefit-risk balance by prescribers. In any case, such far-reaching changes should under no circumstances be implemented without prior testing and validation.

3. We are concerned about the apparent redundancy of the proposed content, which will both increase the overall physical size of the package insert and make retrieval of relevant information unnecessarily cumbersome. As written, the guidance appears to suggest the creation of multiple sections containing repetitive information; this is especially true of the *Overview of the Content and Format of the Adverse Reaction section,* which appears to contain at least some of the same information required in the proposed *Overview of the Content and Format* of the overall package insert, and may also contain information presented in other sections, e.g.,Warnings, Precautions, Drug Interactions, etc. Thus, prescribers will be faced not only with a package insert format containing a general overview, a table of contents, and the body of the insert, but also with an additional overview for the Adverse Reaction section, the complete Adverse Reaction section itself, and any additional safety information included in other sections. It is not clear how these various sections will be related to one another or where a prescriber will find any given piece of safety information.

4. FDA is recommending that relatively long "generic type" statements (e.g. II, B, *1. Statement Concerning the Significance of Adverse Reaction Data Obtained from Clinical Trials* and II, B, 7. *Adverse Reaction Information from Spontaneous Reports)* be included in every product label. There is concern that these statements, may be of limited clinical value, and may be ignored by prescribers since they will appear in every package insert. As stated above in regard to redundant presentation of information, these, and possibly other "generic type" statements, will add to the length of the insert without enhancing its clarity and are thus contrary to the intent of improving the utility of the information presented to the prescriber.

5. The presentation of safety information in a uniform format across disparate products may lead prescribers to conclude that the data themselves are comparable. However, different companies have different methods for data collection and analysis, which currently precludes comparison of safety information between different package inserts for comparable products, information that would be valuable to prescribers in making benefit-risk decisions. It might be misleading to present safety information in a way that suggests comparability when in fact the methods of data acquisition and analysis render the data non-comparable. FDA therefore needs to address not only the presentation format of safety information in labeling but also the consistent collection and analysis of data from company to company, and must also ensure as far as possible that individual reviewing divisions apply logical and consistent processes and criteria for safety data inclusion and presentation across therapeutic classes. One particular area for potential improvement is the application of standardized definitions of specific conditions to mitigate the confounding of information resulting from non-uniform reporting; e.g., an identical constellation of clinical signs and laboratory results may be categorized by one reporter as hepatitis, by another as abnormal liver function, by a third as elevated aminotransferases and bilirubin, etc. The current practice of representing such reports in safety databases strictly in accordance with the subjective reported term results in fragmentation of essentially similar information and consequent loss of clinical utility. Manufacturers and FDA should collaborate in the development of harmonized definitions of terms such as those illustrated to enhance the clinical value of, and minimize the effect of subjectivity on safety terms included in labeling.

6. While this guidance does contain useful general recommendations, some of them are not adequately defined, tend to be vague and, in a few cases, may be misleading. It will therefore be necessary for all terms used in the guidance that do not have internationally agreed definitions to be clearly defined, preferably in full accord with established international standards (e.g. CIOMS, ICH, EU SmPC guidelines). A complete and detailed glossary is needed in the final document. However, definitions *per se* are not necessarily sufficient. One critical example is the use of the term "Adverse Reaction" *(reasonably associated with the use of a drug)* vs. "Adverse Event" *(whether or not considered drug-related)*. While internationally agreed definitions exist for these terms, there is no agreement, regulatory, clinical, or conceptual, regarding the criteria which distinguish an event from a reaction, i.e., when the balance of probability favors a causal association. Before FDA can require labeling to include only adverse reactions, and not adverse events, there must first be standardization and uniform application of criteria which permit their differentiation, i.e., standardized assessments of causality across products and FDA divisions, preferably in an internationally harmonized standard.
   In our experience, it is frequently not possible to distinguish adverse reactions from among the events recorded in clinical trial databases because of confounding by indication, co-morbidity,

or other characteristics of the study population itself, even when the therapeutic indication under study permits the conduct of placebo-controlled studies, which represent a minority of those conducted by our company. Investigator assessments of causality are, by nature, subjective and are often inaccurate, *vide* the number of "adverse drug reactions" reported among placebo-treated patients. It is not clear how an accurate determination of causality could be made in studies using active controls or multiple drug treatments, or in long-term uncontrolled studies, which may reveal adverse events not detectable with relatively brief exposure. Furthermore, as well-recognized (e.g. CIOMS-III, second edition), pre-approval studies are typically designed with statistical power to detect significant differences from placebo or established therapies in predetermined efficacy parameters, but not in safety parameters. It is therefore often difficult, and frequently impossible, to discriminate reliably between observed adverse events that are attributable to the study drug vs. those that are due to the underlying disease, or to another cause entirely.

Since, at this time, in our opinion it is not possible in the majority of cases to differentiate clearly between adverse reactions and adverse events, we suggest that the label should generally present "Adverse Events". The term "Adverse Reactions" used in current labeling regulations is not appropriate, as it suggests that all reported events are in fact attributable to the study drug. This is particularly problematic for the section describing spontaneous post-marketing reports (where establishment of causality is difficult, if possible at all), which, although considered reactions for expedited reporting purposes, are nevertheless categorized by FDA in its own documents as being of unknown causality for clinical analysis purposes. It may be misleading to prescribers, and may provide a confusing picture of the benefit-risk balance, if clinical trial data were included according to one set of criteria and post-marketing data with different criteria. In addition, if commonly observed adverse events were to be added to the post-marketing safety section without being described in the clinical trial experience, this would potentially misrepresent the safety profile.

7. Until such time as a uniform, agreed standard for assessment of drug causality of adverse events is developed, there are two further reasons why it remains desirable to include in the label all common adverse events, not just those judged to be attributable to study drug.

   First, the label should contain all the information a prescriber requires to assess the benefits and risks of the product in a given patient, and thereby optimize the appropriateness of the treatment. The inclusion of safety information must therefore be driven by the utility of that information in enabling health professionals to balance risks against benefits in making therapeutic decisions. They cannot do this without an appreciation of the totality of the events observed during development, including both those that may and those that may not be related to the drug. In particular, if a prescriber needs to assess the likelihood that an observed adverse event may in fact be related to the drug, and might consequently necessitate a change of therapy, it is essential to present the observed incidence of that event in the overall patient population. In this context, it is important to note that the majority of adverse events reported spontaneously in clinical practice are qualitatively and quantitatively similar to those reported in clinical trials, regardless of any presumptive causal association or lack thereof. Inadequate information concerning these common adverse events could result in discontinuation of effective therapy based on a misperception of risk with the consequence that patients could be inappropriately deprived of significant therapeutic benefits. Therefore, excluding events that occur with a rate similar to placebo may

adversely affect a prescriber's ability to make an appropriate therapeutic choice and the proposal to exclude these events requires considerable additional review and discussion prior to possible implementation.

The second reason for including common adverse events not necessarily attributable to drug pertains to another function of labeling, viz. the requirement for regulatory reporting of adverse events. Current FDA practice is to avoid unnecessary reporting of adverse events that do not affect the benefit-risk balance, i.e. those that are non-serious and labeled. It is also good pharmacovigilance practice to apply the closest scrutiny to those events that represent possible new risks to patients, typically serious, unlabeled events. As stated previous, in our experience the reporting pattern of spontaneous adverse events tends to reflect the adverse events reported from clinical trials. The elimination from labeling of adverse events that occur commonly in clinical trials will necessarily result in a marked increase in the number of adverse events that will need to be considered unlabeled, and hence in their regulatory reporting, which will adversely affect both manufacturers and FDA. In particular, serious adverse events that occur commonly in conditions such as diabetes, cancer, infections, heart failure, etc., would require expedited reporting if they were not included in the labels for products used in their treatment, greatly increasing the volume of irrelevant alert reports and potentially seriously compromising the ability of manufacturers and FDA to conduct appropriate pharmacovigilance by markedly decreasing the "signal to noise" ratio. However, if despite this obvious difficulty FDA should eventually decide to limit included safety information to suspected adverse reactions only, BMS recommends that some alternative approach be devised to eliminate from regulatory reporting adverse events that occur frequently in the treated population and at comparable rates in both drug and control groups, which are currently considered as expected according to existing labeling standards. For example, an additional section of the label could be created to contain those common events that would be considered "expected" for the purposes of regulatory reporting, or the label might omit those events while the manufacturer and FDA agreed at the time of an NDA approval what common events would be considered expected.

BMS considers that taking all the foregoing issues into account, the label should include the totality of the safety experience observed with the product in clinical trials.

8. Information regarding medical interventions for an adverse reaction is not routinely contained in labeling and many companies may not even capture this type of information. Thus, obtaining this information might require considerable re-engineering of the processes and procedures used in clinical development programs and, in particular, will not be available for a large proportion of post-marketing reports.

9. FDA's proposed use of established CIOMS definitions for adverse event frequency has been accepted by other regulatory authorities internationally and may add some value to the relative evaluation of the safety information by the prescriber. However, rare and very rare events are unlikely to be observed among the relatively small number of subjects in clinical trials, and if they are will almost certainly not be capable of adequate characterization because of the limited number. It is also unclear how these two categories might be applied to the description of adverse event frequency, since actual numerators and denominators are not available for spontaneously reported post-marketing events, the principal mechanism for detecting rare and very rare events. Many manufacturers, including BMS, conduct formal epidemiological studies post-approval precisely in order to derive accurate incidences of rare but important adverse events; FDA should provide guidance on the appropriate method and format for including the results of such studies in labeling.

10. The proposal to present adverse event incidences rounded to the nearest integer creates a significant likelihood for a misleading presentation of the data, especially when the size of the study population varies significantly among different products, leading to potential misconception of the incidence of an adverse event. Mandatory rounding up to 1% may affect the placement of particular events in tables vs. text. It will also be necessary to take into account the varying granularity of adverse event coding dictionaries, since incidences of individual AEs will be affected by the coding terminology applied, e.g. COSTART vs. MedDRA. This concern is discussed further in section III.

11. Further clarification is requested concerning the scope and the time frame for implementation of the new format. FDA should specify whether it will apply to new chemical entities only, supplemental NDAs for approved products, or even to established labeling for existing products. It will be difficult, if not impossible, to convert the majority of current labels into the new format, especially in regard to the potential removal of those Adverse Events that are not considered Adverse Reactions, which would require significant resources for re-analysis of data (if even available in a format suitable for analysis, especially for older products with a well-established safety profile) for a result of potentially little or no clinical value to the prescriber. For these reasons, BMS recommends that the new label format be applicable to new chemical entities only, and an appropriate lead time prior to implementation needs to be defined to permit manufacturers to revise, if necessary, existing procedures for clinical trial safety data collection and analysis to comply with the proposed changes in data selection and presentation.

12. A significant commercial concern for industry will be how labeling of existing products would be viewed in comparison with newly approved products with the new labeling format. This could result in either a competitive advantage or disadvantage, depending on the relative presentation of the safety information in the respective labels (e.g., new products might be erroneously perceived as having either a better, or worse, safety profile than older competitors). Prescribers will need instruction concerning the implications of the apparent differences, and FDA will need to provide specific guidance prior to implementation on what manufacturers may or may not promote concerning these differences.

Specific Comments on Each Section

I. Introduction

FDA is proposing that the determination of which adverse events to include in the Overview is critically dependent on individual judgement. This position does not differ substantially from that in effect currently, and it is not clear how the assessment factors of "seriousness, severity, frequency, and strength of causal association" will be applied across widely differing indications for treatment with very different benefit-risk balances. The CIOMS III document has presented a series of evaluation criteria for determination of causality, although it is not clear how well those criteria work in practice. BMS recommends that FDA and industry conduct a joint evaluation of those criteria as a starting point for the development of a uniform approach to the assessment of causality. The availability of a set of standardized causality assessment tools would address many of the issues this draft guidance raises.

II. Adverse Reactions Section - Content and Format

Section A - Overview - Content and Format

The draft guidance states that the Overview section will highlight information on "serious and important" adverse reactions. These terms are undefined and require regulatory definition through normal procedures. It is also unclear what subset of the overall adverse events would qualify as "most important to prescribing decisions and to observing, monitoring, and advising patients." By implication, any safety information that is represented only in the body of the Adverse Events section would then be considered less or not "important to prescribing decisions and to observing, monitoring, and advising patients", raising the question of its inclusion in the label at all. As noted previously, the manufacturer and FDA will be forced to select from among the entire body of all safety information certain "serious and important adverse reactions". This not only leads to redundant presentation of the data but also to a potential for undue exposure of the manufacturer to product liability lawsuits based on a "failure to warn" if a given event is listed in the overall adverse event experience section, but not in the overview section. If FDA nevertheless mandates an "overview", then at a minimum, the criteria for selecting the relatively small subset of events for presentation in the Summary section must be clearly specified to avoid arbitrary assessment of "importance" by the manufacturer and/or FDA.

Finally, the existence of an adverse event summary section creates the very real potential danger that time-pressured prescribers will refer only to it, ignoring the remaining safety information.

It should be noted that "adverse reactions most frequently resulting in clinical intervention" is not something that is commonly analyzed for all patients. This is usually reported in the clinical trial database only for discontinuations. This information is even less likely to be available for spontaneous reports.

Section B - Discussion of Adverse Reactions Information - Content and Format

1. Statement Concerning the Significance of Adverse Reaction Data Obtained from Clinical Trials

As noted above, it is not clear what value the use of boilerplate language adds. The use of the phrase "widely varying conditions" implies an uncontrolled environment, and should be deleted. If the data presented comprise Adverse Events rather than Adverse Reactions, the last sentence becomes inappropriate (i.e., related to drug use). The final phrase "for approximating rates" is not well defined and essentially contradicts the earlier statement that the rates given are not comparable. However, if this type of formulaic language is to be used, we recommend a statement along the following lines:

"*Clinical trials are conducted under varying conditions; consequently, adverse event rates observed in clinical trials of one drug cannot be directly compared to rates in clinical trials of another drug, and the incidence of adverse events in trials may not reflect the event rates encountered in clinical practice.*"

2. Description of Data Sources

The draft guidance states that "...the description should discuss the rationale for not basing rates on all reported events." This final sentence appears to contradict recommendations presented elsewhere in the document for providing the incidence of related events ("reactions") only, and it is not clear why justification is requested for omission of adverse events deemed unrelated to study drug when the focus of the entire document is on adverse reactions. Since the use of MedDRA terms will reduce the incidence of many adverse events compared with their presentation in older, more coarsely granular terminologies,specific incidence thresholds should be avoided if MedDRA is used. As stated elsewhere in these comments, the exclusion of events occurring more commonly with placebo may not be appropriate.

The terms "critical exclusions from" and "unusual components of" the safety database should be clearly defined.

3. Tabular Presentation of Adverse Reaction Data

If active-controlled data are informative, they should not necessarily be excluded from the label even if placebo-controlled and/or dose-response data are available.

4. When Additional Tables May be Needed

"There will almost always be differences in the rates of adverse reactions from different sources and population subsets, but these differences are typically not important". This is a rather sweeping statement which is frequently not borne out in actual experience. As stated later in this section, a new indication in a different patient population can produce a very different adverse event profile; the second sentence of this section does not present useful information, and we therefore suggest deleting it.

5. Commentary and Elaboration on Tabular Data

Much of the adverse event narrative section will be duplicative if the same information is included in other sections, e.g., Warnings or Precautions.

The Discussion of Clinically Important Adverse Reactions subsection states that "the commentary should discuss the intervention that is indicated". This appears to extend beyond the scope of product information and into the sphere of standard medical practice. Since standards of medical practice change rapidly, ensuring that this section of the label is current poses a very considerable challenge both for manufacturers and FDA. Therefore, unless there are any specific interventions that are required for specific clinical situations (e.g. a specific antidote, hemodialysis, or gastric lavage for an overdose), this proposal raises serious concerns for having to address all interventions (including dose reduction, dose increase, therapy discontinuation, etc.) that could possibly be required. Additionally, neither the manufacturer nor FDA is in a position to inform the prescriber what the appropriate intervention should be in any given patient or to keep the label current in the face of the constantly changing practice of medicine.

The "Duration of Treatment" section is confusing as written. There is no definition of "continued" or "long-term" use. Does this section refer to data obtained in continuing or new post approval clinical trials, to spontaneous data from marketed use, or both?

"Subpopulation and Risk Factor Data" - Usually, patients with significant hepatic and renal impairment are excluded from clinical trials, and reliable information concerning these populations can be obtained only from specially targed studies, which can however typically be conducted only in very small numbers of subjects. It should also be noted that it is almost never possible to obtain "reliable negative information" with any reasonably sized clinical trial. Similarly, ascertaining the true incidence of adverse events in subjects receiving concomitant medications is extremely difficult because of the relatively uncontrolled nature of most concomitant therapy. This type of information is more readily available from epidemiological studies conducted after marketing, and the guidance should address the circumstances under which the results of such studies may be included in the label.

Under "Vital Signs", the draft guidance states that labeling should usually include information on vital sign measurements "if relevant and not provided elsewhere...". An example of what is intended would help to clarify the intent of this statement.

6. Presentation of Less Common Events

BMS concurs in principle with the statement that "Long and exhaustive lists of adverse events ... should be avoided". However, as mentioned previously, "events that are commonly observed in the absence of drug therapy, or not plausibly related to drug therapy" are among the most frequently reported in post-marketing surveillance, and will require either periodic or expedited reporting to FDA if they are considered "unlabeled" or "unexpected", which we believe does not best serve the protection of the public health.

This section recommends inclusion of events that are "serious but very unusual in the absence of drug therapy ... even if there are only one or two reports." While this approach does have merit, an objective assessment of causality as described above is essential before listing the event in the label. If not, labeling will be based on subjective assessment of individual case reports, rather than on an objective assessment of the totality of the evidence.

BMS does not believe that adverse events from clinical trials and spontaneous reports should be presented in the same listing, as their level of clinical validity differs, and comparative information is not available for spontaneous reports. As previously stated, spontaneous reports may be considered to be adverse reactions, i.e., drug-related, for regulatory reporting purposes, but not for clinical evaluation in the vast majority of cases, as also stated in section 7 of the draft. Therefore, if FDA maintains the position that only drug-related events from clinical trials should be included, spontaneous reports must obviously be described separately, with an appropriate disclaimer such as that in section 7 of the draft.

7. Adverse Reaction Information from Spontaneous Reports

The proposed statement requires revision. As we have stated elsewhere, it is indeed "not always possible to reliably... establish a causal relationship"; this is a very significant understatement, as it is the exception rather than the rule for the vast majority of spontaneous reports to be able to establish any causal relationship to drug. Based on this premise, inclusion of spontaneously reported events in the label based on "strength of causal connection" will be very infrequent. Furthermore, FDA's statement that "it is not always possible to reliably estimate their frequency", again massively understates the problem; it is almost never possible to obtain a reliable estimate of incidence from spontaneous reports, and frequency of reporting is affected by many confounding factors, including media publicity. As stated previously for clinical trial events, standardization of causality evaluation criteria is a *sine qua non* for rational assessment of spontaneous reports prior to inclusion in the label.

It is clearly necessary to include in the label safety information obtained in the clinical practice setting. However, this must be done using terminology that accurately reflects the uncertainty surrounding the reported information. BMS therefore suggests wording along the following lines:

"The following Adverse Events have been reported during postapproval use of [drug name]. The following caveats should be borne in mind when considering these events as potential adverse reactions to [drug name]: reporting is voluntary and the ratio of reported to observed events is unknown; the reports often contain incomplete information, and may not be clinically validated; the size of the patient population treated with [drug name] is uncertain; and identified or unidentified confounding factors (e.g. co-morbid conditions, concomitant therapy) are often present. For these reasons, it is not possible to reliably estimate their frequency or establish a causal relationship to [drug name]".

III - Organizing and Presenting Adverse Reactions Data in a Table

Body System Organization: - FDA should consider the impact of using MedDRA on labeling. The issues include standardizing the order of listing of events by System Organ Class and what level of the hierarchy, if any, will be presented. In this context, it is essential to note that frequencies of adverse events, especially common adverse events, will differ markedly in MedDRA from those in older, more coarsely granular, terminologies, hence existing criteria for inclusion of adverse events based on incidence thresholds will not apply. While it may be possible in a few cases to use MedDRA hierarchical aggregation terms (HLGTs and HLTs) for labeling, it should be noted that many of those terms are unsuited to labeling use, as they do not express safety information in natural medical language intelligible to the average prescriber. Also, to date MedDRA has not to our knowledge been used by any manufacturer or regulatory authority for labeling purposes, and any proposal to do so should be deferred until such time as MedDRA has been properly evaluated for that purpose. BMS considers that labels should describe safety information using natural medical language, regardless of any specific analytical tool used for its derivation, and opposes requiring the use in labeling of any terminology or coding system that does not allow the expression of safety information in terms used in conventional medical practice and clearly intelligible to the average practitioner.

Comparator Adverse Reaction Data: This section states that placebo "or other comparator arms" should be included in the table. Section II 3, however, suggests that only placebo-controlled data should be presented in tabular format. FDA should clarify and expand on this.

Percentages: Rounding to the next integer can lead to inappropriate presentations of the data. For instance, a placebo incidence = 0.51% would be rounded to 1% and a study drug incidence = 1.49 % would also be rounded to 1%. If the study population is sufficiently large that this represents a true difference, in this instance rounding obliterates the potential clinical significance. Also, reporting AEs with a frequency of at least 1% would lead to also reporting those adverse events with incidence of 0.51% which is < 1%. These computations also do not take into account the impact of the granularity of MedDRA Preferred Terms (PTs); many adverse events, which exceed a given arbitrary threshold incidence using prior terminologies, such as COSTART, will fall below it if MedDRA PTs are used for data presentation. Since there is no experience to date with the use of MedDRA for the presentation of clinical trial adverse event data, any numerical specification of thresholds for inclusion should be qualified with a statement that "These thresholds have been determined using coding dictionaries such as COSTART, and may not be applicable to adverse events coded using a more specific terminology, such as MedDRA."

IV - Presenting Data in the Adverse Reactions Section of Labeling

"Selection or exclusion of adverse events for presentation in the ADVERSE REACTIONS section should be based on factors such as frequency of reporting, whether the adverse reaction rate for drug exceeds the placebo rate, etc." We have previously provided reasons why this approach may not always be appropriate. The issue of trials in which placebo controls are not possible is not addressed.

Rare, Serious Events: there is again inconsistency in usage of the terms "reactions" rather than "events". The last word in this section should apparently be "cases" ("...even if there are only one or two reported cases."). As stated previously, standardized assessments of causality are a necessity for the proper evaluation of such cases.

Determining Adverse Reaction Rates: BMS concurs that investigator judgment is not an appropriate criterion for assessing causality.

Characterizing Adverse Reactions: BMS suggests that generally accepted terms such as those defined in the CIOMS III document are appropriate for use in describing adverse event frequency, subject to the caveats expressed previously.

V - Updating the Adverse Reactions Section of Labeling

Inconsistent or Outdated Information: The term "defects" is inappropriate, and should be omitted. By definition, a label reflects the best understanding of the manufacturer and FDA of the supporting data available at the time any given version is agreed. Labeling should evolve over time as additional data become available, but in no case should there be "any *defects* in labeling that may have accumulated with time". The adoption of PSURs as specified in the ICH E2C guideline would ensure complete review of the currency of product labeling at regular intervals consistent with the maturity of the product. The last sentence is misleading, since the responsibility for updating labeling is legally shared by the sponsor and FDA, both of whom are required to monitor evolving drug safety and propose modifications necessary to protect the public health. In this context, it should be noted that it is solely FDA's responsibility to ensure uniformity among different companies' labeling, especially class labeling. As stated previously, many manufacturers, including BMS, conduct formal epidemiological studies post-approval to address specific safety issues that were not observed or inadequately characterized in clinical trials or from available post-marketing case reports. BMS requests that FDA provide guidance to address the following issues arising from such studies:

- What is the appropriate presentation format in labeling of epidemiological study results, both in terms of absolute risk for the product in question, as well as its comparative risk in relation to other therapies? This is particularly important for negative findings, when an appropriately-conducted epidemiological study demonstrates that the incidence of an event previously included in the label as a possible "reaction" does not differ from the background rate in the target population.

- How should broader issues of comparative benefit-risk balances between different products be included?

Glossary:
All terms used in the Guidance that do not have agreed definitions should be included in the Glossary (e.g., "important adverse reactions", "critical exclusion", "unusual components").

Conclusion:

The draft guidance is potentially a major advance in improving the quality of the information presented in the Adverse Reactions section. However, to avoid multiple updates to the labeling, no date should be set for its implementation prior to the availability of the promised FDA guidances for changes to the format and content of other sections of the label that present important aspects of safety information (i.e., Contraindications, Warnings and Precautions) as well the revision to the "Overall Format and Content" of the label. It is also extremely important for ease of use by prescribers that redundancy between sections and the inclusion of qualifying statements be minimized.

BMS considers that the proposal to distinguish between Adverse Reactions and Adverse Events may have merit, but that its application to clinical trial and especially post-marketing data is fraught with uncertainty and ambiguity. Until there is general agreement on the specific criteria for establishing drug causality of adverse events, preferably in an internationally harmonized approach, BMS believes that the overall rate of Adverse Events is the most appropriate descriptor of the observed safety profile of the product. We also suggest that the presentation of events occurring with an incidence equivalent to placebo or other active comparator agent provides information of value to the prescriber and therefore should generally be included in labeling.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

Laurie Smaldone, M.D
Senior Vice President
Regulatory Sciences & Outcomes Research

From: NANCY E. CALL (609)252-5710
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